Is there evidence for an autoimmune response to components of the TGF-β signalling pathway in scleroderma?

Sirs,

Vascular involvement is prominent in systemic sclerosis (scleroderma), yet the pathogenesis of vascular injury remains incompletely understood. There is evidence that a defect in angiogenesis is responsible for scleroderma vascular disease. Endoglin, a transmembrane auxiliary receptor for transforming growth factor-beta (TGF-b) expressed on endothelial cells, plays a critical role in angiogenesis and response to vascular perturbation. During inflammation, endoglin is cleaved; the released soluble protein acts as a scavenger of specific TGF-b family ligands (*e.g.* BMP9), thus altering angiogenesis (1). Elevated soluble endoglin levels are reported in scleroderma and associate with telangiectasias and pulmonary arterial hypertension (PAH) (2). Cutaneous telangiectasia develops in patients with cancer treated with anti-endoglin antibodies (3).

Along with endoglin, several mutations involving other members of the ALK1/BMPII axis, including BMP9, cause heritable PAH (4). In mouse models, BMP9 administration prevents and reverses PAH (5). These data suggest that an autoimmune process affecting TGF-β signalling by targeting endoglin and/or BMP9 could underlie the angiogenesis defect in scleroderma.

In this study, approved by the Johns Hopkins IRB, we investigated whether antibodies against endoglin and/or BMP9 were present in a well-defined subgroup of patients with scleroderma and prominent vascular involvement. We identified patients in the Johns Hopkins Scleroderma Center Research Registry with documented telangiectasia on exam. Forty patients with a high cutaneous telangiectasia burden were selected for inclusion. ELISA assays were set up to detect these antibodies using previously described methods (6). Briefly, wells of 96-well plates were coated with 50 ng/well of recombinant human endoglin (SinoBiological no. 10149-H08H) or BMP9 (Abcam no. 94350) and sera were tested at 1:150 or 1:200 dilution (endoglin and BMP9 ELISAs, respectively). Anti-endoglin antibodies were not detected (0/15 healthy control sera, and 0/40 scleroderma case sera). Similarly, anti-BMP9 antibodies were not detected (0/13 healthy controls, and 0/40 scleroderma cases). A subset of the case sera (n=5) and healthy controls (n=3) were subsequently tested for anti-BMP9 antibodies by immunoprecipitation from HeLa lysate, followed by blotting with an anti-BMP9 antibody (Genetex no. 108417). While BMP9 was robustly detected in the input lysate, none of the sera tested immunoprecipitated BMP9.

While this study did not detect these antibodies by ELISA, it does not exclude the possibility that an autoimmune process could target other components of the TGF-β signalling pathway and its family of ligands.

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